L2 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:136698 HCAPLUS
DOCUMENT NUMBER: 136:395185
TITLE: Non steroidal anti-inflammatory and anti-allergy agents
AUTHOR(S): Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54006, Greece
SOURCE: Current Medicinal Chemistry (2002), 9(1), 89-98
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used for inflammation therapy. The major drawback in using the NSAIDs is in their tendency to cause gastrointestinal toxicity. Since the roles of arachidonic acid (A.A) metabolites, as leukotrienes (Lts), prostaglandins (PGs) and thromboxanes (TXA2) as mediators of the inflammatory reaction were clarified, much effort has been made to develop inhibitors of the prodn. of these chem. mediators as anti-inflammatory agents. These mediators also play important roles in some inflammatory or allergic diseases, acting either alone or in combination and inhibitors of 5-lipoxygenase (5-LOX) and/or cyclooxygenase isoforms 1,2 (COX-1,2) may be useful for the treatment of **asthma**, psoriasis and rheumatoid arthritis. Leukotrienes, the products of 5-LOX metab. have been assocd. with immediate hypersensitivity reactions, anaphylaxis and **asthma**. In addn., active oxygen species (AOS) including superoxide anion (O2-), hydrogen peroxide, hydroxyl radical and ferric radical, mediate cell damage in a variety of pathophysiol. conditions and are responsible for oxidative injury of enzymes, lipid membranes and DNA in living cells and tissues. Prostaglandins and leukotrienes in the arachidonate pathway linked with lipid peroxidn. may amplify the oxidative damage. Nitric oxide (NO) plays also a role as an effector in inflammation, since PG and NO thought to be important in maintaining mucosal integrity. Dual or selective inhibitors, specific receptor antagonists, AOS scavengers, and NO donors have been under development for therapeutic application. Several classes of inhibitors have been identified and at least 12 major chem. series are known to affect PGs prodn. directly. In this review, we account on our research work concerning NSAIDs combined with a ref. of the recent literature.

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25604 ASTHMA?
L1 135 COX-2 AND ASTHMA?

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1741568 REVIEW/DT
L2 22 L1 AND REVIEW/DT

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Full Text | Citing References

ACCESSION NUMBER: 2003:969624 HCAPLUS
DOCUMENT NUMBER: 140:12337
TITLE: **COX-2** specific inhibitors in NSAID-intolerant patients
AUTHOR(S): Picado, C.
CORPORATE SOURCE: Servei de Pneumologia i Allergia Respiratoria, Institut Clinic de Panumologia i Cirurgia Toracia, Hospital Clinic, Department de Medicina, Universitat de Barcelona, Barcelona, 08036, Spain
SOURCE: International Journal of Immunopathology and Pharmacology (2003), 16(2, Suppl.), 11-16
CODEN: IJIPE4; ISSN: 0394-6320
PUBLISHER: Biolife s.a.s.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Most adverse NSAID-induced respiratory and skin reactions appear to be pptd. by the inhibition of cyclooxygenase-1 (COX-1); this in turn activates the lypoxygenase pathway, which eventually increases the release of cysteinyl leukotrienes (Cys-LTs). Recent studies have reported that patients with NSAID-induced **asthma** have a low prodn. of PGE2 in respiratory epithelial cells, bronchial fibroblast and peripheral blood cells. Low prodn. of PGE2 may be due to an insufficient cyclooxygenase-2 (**COX-2**) expression in the inflammatory response underlying **asthma**. Since PGE2 administered by inhalation inhibits NSAID-induced bronchoconstriction and the parallel increase in Cys-LTs release, a reduced PGE2 synthesis may render NSAID-patients more susceptible to the COX-1 inhibitory effects of NSAIDs. Recent studies have shown that selective **COX-2** inhibitors (rofecoxib and celecoxib), unlike COX-1 inhibitors, are very well tolerated by NSAID-sensitive patients and do not elicit increased Cyst-LTs prodn. However, these drugs can still can ppt. cutaneous reactions in a significant proportion of patients with skin reactions to NSAID. The heterogeneity of the NSAID-intolerance syndrome suggests that subjects who do not tolerate NSAID can use coxibs only after first having been exposed to the drug under the supervision of a specialist with experience in these procedures.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2003:839655 HCAPLUS
DOCUMENT NUMBER: 139:357854
TITLE: Safety of **COX-2** inhibitors in **asthma** patients with aspirin hypersensitivity
AUTHOR(S): West, Patricia M.; Fernandez, Cristina
CORPORATE SOURCE: Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA
SOURCE: Annals of Pharmacotherapy (2003), 37(10), 1497-1501
CODEN: APHRER; ISSN: 1060-0280
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Objective: To review the safety of cyclooxygenase-2 (**COX-2**) inhibitors in **asthma** patients with aspirin hypersensitivity. Data Sources: Clin. studies were identified using MEDLINE (1966-Sept. 2002). Key search terms included cyclooxygenase inhibitors, aspirin, **asthma**, and hypersensitivity. English-language articles were identified and included. Refs. from the identified articles were also reviewed. Data Synthesis: The literature provides information regarding the safety of **COX-2** inhibitors in **asthma** patients with aspirin-exacerbated respiratory disease (AERD). The mechanism of AERD involves inhibition of cyclooxygenase, particularly COX-1. Inhibition of COX-1 causes an increased prodn. of certain inflammatory mediators, which results in the reactions seen with AERD. Considering this mechanism, **COX-2** inhibitors may be an alternative to aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) in a patient with AERD. This article analyzes 4 studies to evaluate the safety of **COX-2** inhibitors in this population. Results: The 4 studies evaluated included a total of 172 patients with AERD. All patients included demonstrated intolerance to aspirin or NSAIDs and tolerated the selective **COX-2** inhibitor administered. Conclusions: **COX-2** inhibitors provide a potentially safe alternative for treatment of inflammatory conditions in patients with AERD.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:490204 HCAPLUS
DOCUMENT NUMBER: 139:196694
TITLE: n-3 polyunsaturated fatty acids and inflammation: From molecular biology to the clinic
AUTHOR(S): Calder, Philip C.
CORPORATE SOURCE: Institute of Human Nutrition, University of Southampton, Southampton, SO16 7PX, UK
SOURCE: Lipids (2003), 38(4), 343-352
CODEN: LPDSAP; ISSN: 0024-4201
PUBLISHER: AOCS Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The immune system is involved in host defense against infectious agents, tumor cells, and environmental insults. Inflammation is an important component of the early immunol. response. Inappropriate

or dysfunctional immune responses underlie acute and chronic inflammatory diseases. The n-6 polyunsatd. fatty acid (PUFA) arachidonic acid (AA, C20:4n-6) is the precursor of prostaglandins, leukotrienes, and related compds. that have important roles in inflammation and regulation of immunity. Feeding fish oil results in partial replacement of AA in cell membranes by eicosapentaenoic acid (EPA, C20:5n-3). This leads to decreased prodn. of AA-derived mediators, through several mechanisms, including decreased availability of AA, competition for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, and decreased expression of **COX-2** and 5-LOX. This alone are potentially beneficial anti-inflammatory effects of n-3 FA. The n-3 PUFA have a no. of other effects that might occur down-stream of altered eicosanoid prodn. or might be independent of this effect. Dietary fish oil can suppress the prodn. of proinflammatory cytokines and can modulate adhesion mol. expression. These effects occur at the level of altered gene expression. Fish oil feeding can ameliorate the symptoms of autoimmune disease in some animal models and protect against the effects of endotoxin. Clin. studies show that oral fish oil supplementation has beneficial effects in rheumatoid arthritis and in some **asthmatics**, supporting the idea that the n-3 PUFA in fish oil are anti-inflammatory. There are indications that the inclusion of fish oil in enteral and parenteral formulas is beneficial to patients.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2003:425591 HCAPLUS
DOCUMENT NUMBER: 139:373869
TITLE: Aspirin-induced **asthma**: Advances in pathogenesis, diagnosis, and management
AUTHOR(S): Szczeklik, Andrew; Stevenson, Donald D.
CORPORATE SOURCE: Department of Medicine, Jagellonian University, Krakow, Pol.
SOURCE: Journal of Allergy and Clinical Immunology (2003), 111(5), 913-921
CODEN: JACIBY; ISSN: 0091-6749
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. In some **asthmatic** individuals, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase 1 (COX-1) exacerbate the condition. This distinct clin. syndrome, called aspirin-induced **asthma** (AIA), is characterized by an eosinophilic rhinosinusitis, nasal polyposis, aspirin sensitivity, and **asthma**. There is no in vitro test for the disorder, and diagnosis can be established only by provocation challenges with aspirin or NSAIDs. Recent major advances in the mol. biol. of eicosanoids, exemplified by the cloning of 2 cysteinyl leukotriene receptors and the discovery of a whole family of cyclooxygenase enzymes, offer new insights into mechanisms operating in AIA. The disease runs a protracted course even if COX-1 inhibitors are avoided, and the course is often severe, many patients requiring systemic corticosteroids to control their sinusitis and **asthma**. Aspirin and NSAIDs should be avoided, but highly specific **COX-2** inhibitors, known as coxibs, are well tolerated and can be safely used. Aspirin desensitization, followed by daily aspirin treatment, is a valuable therapeutic option in most patients with AIA, particularly those with recurrent nasal polyposis or overdependence on systemic corticosteroids.

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR

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Full Text | Citing References

ACCESSION NUMBER: 2003:285832 HCAPLUS
DOCUMENT NUMBER: 139:66864
TITLE: Transcriptional regulation of **COX-2**: a key mechanism in the pathogenesis of nasal polyposis in aspirin-sensitive **asthmatics**?
AUTHOR(S): Vignola, A. M.; Bellia, V.
CORPORATE SOURCE: Istituto di Medicina Generale e Pneumologia, Universita di Palermo, Palermo, 180 90146, Italy
SOURCE: Allergy (Oxford, United Kingdom) (2003), 58(2), 95-97
CODEN: LLRGDY; ISSN: 0105-4538
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review on the role of cyclooxygenase 2 (**COX-2**) in aspirin-sensitive rhinitis and **asthma**. A diminished expression of **COX-2** has been found in nasal polyps from aspirin hypersensitivity **asthma** or rhinitis subjects. **COX-2** downregulation is assocd. with a decreased expression and activation of the transcription factor NF-κB. This finding may provide a mechanistic explanation of the reduced **COX-2** expression in nasal mucosa of aspirin-sensitive subjects, and highlight the potential involvement of the NF-κB system in the pathogenesis of chronic rhinosinusitis with nasal polyposis in aspirin-sensitive **asthmatics**.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2003:88686 HCAPLUS
DOCUMENT NUMBER: 139:206771
TITLE: Specific cyclooxygenase-2 inhibitors and aspirin-exacerbated respiratory disease
AUTHOR(S): Crofford, Leslie J.
CORPORATE SOURCE: Division of rheumatology, University of Michigan, Ann Arbor, MI, USA
SOURCE: Arthritis Research & Therapy (2003), 5(1), 25-27
CODEN: ARTRCV; ISSN: 1478-6362
URL: http://arthritis-research.com/content/pdf/ar620.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English

AB A review. The use of analgesic anti-inflammatory agents in patients with **asthma** is clin. challenging because of the prevalence (10-20%) of aspirin hypersensitivity. Aspirin-exacerbated respiratory disease (AERD), or aspirin-induced **asthma**, is characterized by **asthma** and rhinitis triggered by the ingestion of aspirin and non-steroidal anti-inflammatory drugs. AERD is assocd. with upper and lower respiratory-tract mucosal inflammation, progressive sinusitis, nasal polyposis, and **asthma** regardless of whether patients avoid triggering drugs. The mechanism underlying the propensity of aspirin and non-steroidal anti-inflammatory drugs to cause this reaction is thought to involve inhibition of the synthesis of protective prostaglandins (PGs), resulting in an increase in the synthesis of cysteinyl leukotrienes by eosinophils and mast cells.

Clin. data suggest that protective PGs are derived from cyclooxygenase (COX)-1 because studies have now confirmed that drugs specifically inhibiting **COX-2** are not cross-reactive with aspirin in patients with AERD.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:932690 HCAPLUS
DOCUMENT NUMBER: 138:361994
TITLE: Diagnosis, prevention, and treatment of aspirin-induced **asthma** and rhinitis
AUTHOR(S): Bochenek, G.; Banska, K.; Szabo, Z.; Nizankowska, E.; Szczeklik, A.
CORPORATE SOURCE: Department of Medicine, Jagiellonian University School of Medicine, Krakow, Pol.
SOURCE: Current Drug Targets: Inflammation & Allergy (2002), 1(1), 1-11
CODEN: CDTICU; ISSN: 1568-010X
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Bronchial **asthma** is not a homogeneous disease. Several variants of **asthma** can be distinguished. One of them is aspirin-induced **asthma**. In this distinct clin. syndrome, aspirin and most other nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase-1 ppt. rhinitis and **asthma** attacks. This type of **asthma** affects 5-10% of adult **asthmatics**, but remains largely underdiagnosed. The natural history of aspirin-induced **asthma** (AIA) was described, based on an extensive pan-European survey. Aspirin provocation tests with improved diagnostic accuracy were developed, although no in-vitro tests was found to be of diagnostic value. Recent interest in AIA was stirred by the finding of alterations in arachidonate metabolic pathways, leading to cysteinyl-leukotriene overprodn. LTC4 synthase is overexpressed in bronchi and its mRNA is upregulated in peripheral blood eosinophils. The gene coding for LTC4 synthase exists in 2 common alleles, 1 of which appears to be assocd. with a severe, steroid-dependent type of **asthma**. New highly specific **COX-2** inhibitors appear to be a safe alternative for patients with aspirin-induced **asthma**.

REFERENCE COUNT: 141 THERE ARE 141 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2002:331066 HCAPLUS
DOCUMENT NUMBER: 137:362185
TITLE: The role of COX-1 and **COX-2** in **asthma** pathogenesis and its significance in the use of selective inhibitors
AUTHOR(S): Szczeklik, A.; Sanak, M.
CORPORATE SOURCE: Department of Medicine, Jagellonian University School of Medicine, Krakow, 31-066, Pol.
SOURCE: Clinical and Experimental Allergy (2002), 32(3), 339-342
CODEN: CLEAEN; ISSN: 0954-7894
PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, discussing the role of COX-1 and **COX-2** in **asthma** pathogenesis and its significance in the use of selective inhibitors as antiasthmatics, antiallergics, and antiinflammatory agents.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:136698 HCAPLUS
DOCUMENT NUMBER: 136:395185
TITLE: Non steroidal anti-inflammatory and anti-allergy agents
AUTHOR(S): Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54006, Greece
SOURCE: Current Medicinal Chemistry (2002), 9(1), 89-98
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used for inflammation therapy. The major drawback in using the NSAIDs is in their tendency to cause gastrointestinal toxicity. Since the roles of arachidonic acid (A.A) metabolites, as leukotrienes (Lts), prostaglandins (PGs) and thromboxanes (TXA2) as mediators of the inflammatory reaction were clarified, much effort has been made to develop inhibitors of the prodn. of these chem. mediators as anti-inflammatory agents. These mediators also play important roles in some inflammatory or allergic diseases, acting either alone or in combination and inhibitors of 5-lipoxygenase (5-LOX) and/or cyclooxygenase isoforms 1,2 (COX-1,2) may be useful for the treatment of **asthma**, psoriasis and rheumatoid arthritis. Leukotrienes, the products of 5-LOX metab. have been assocd. with immediate hypersensitivity reactions, anaphylaxis and **asthma**. In addn., active oxygen species (AOS) including superoxide anion (O2-), hydrogen peroxide, hydroxyl radical and ferric radical, mediate cell damage in a variety of pathophysiol. conditions and are responsible for oxidative injury of enzymes, lipid membranes and DNA in living cells and tissues. Prostaglandins and leukotrienes in the arachidonate pathway linked with lipid peroxidn. may amplify the oxidative damage. Nitric oxide (NO) plays also a role as an effector in inflammation, since PG and NO thought to be important in maintaining mucosal integrity. Dual or selective inhibitors, specific receptor antagonists, AOS scavengers, and NO donors have been under development for therapeutic application. Several classes of inhibitors have been identified and at least 12 major chem. series are known to affect PGs prodn. directly. In this review, we account on our research work concerning NSAIDs combined with a ref. of the recent literature.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:605206 HCAPLUS
DOCUMENT NUMBER: 136:79046
TITLE: Aspirin, nonsteroidal anti-inflammatory drugs, and

preservatives as causes for severe **asthma**
AUTHOR(S): Stevenson, Donald D.
CORPORATE SOURCE: Division of Allergy, Asthma and Immunology, Scripps Clinic and the Scripps Research Institute, La Jolla, CA, USA
SOURCE: Lung Biology in Health and Disease (2001), 159(Severe Asthma), 361-387
CODEN: LBHDD7; ISSN: 0362-3181
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with refs. discusses the clin. features of aspirin-sensitive **asthma** (ASA) respiratory disease and methods for diagnosing ASA sensitivity. It also covers the prevalence of ASA; cross-reactions with nonsteroidal anti-inflammatory drugs (NSAIDs); lack of cross-reactions with cyclooxygenase-2 (**COX-2**) inhibiting NSAIDs, as well as with other drugs and chems.; the phenomenon of ASA desensitization; and treatment. Comments regarding the severity of **asthma** in ASA-sensitive **asthmatics** are focused in two areas, i.e., respiratory reactions and aspirin respiratory disease.
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:554482 HCAPLUS
DOCUMENT NUMBER: 136:272445
TITLE: The pharmacological profile of ML3000: a new pyrrolizine derivative inhibiting the enzymes cyclo-oxygenase and 5-lipoxygenase
AUTHOR(S): Tries, S.; Laufer, S.
CORPORATE SOURCE: R&D Division, Merckle GmbH, Blaubeuren, 7, 89143, Germany
SOURCE: Inflammopharmacology (2001), 9(1-2), 113-124
CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with refs. Since the discovery of aspirin about one century ago, many non-steroidal anti-inflammatory drugs (NSAIDs) have been used for the treatment of inflammatory states and pain. While the NSAIDs are generally safe and effective, common side effects frequently limit therapy. Typical mechanism-based side effects are gastrointestinal (GI)-related, ranging from GI upset and intolerance to ulceration and bleeding after long-term therapy. In order to overcome these side effects several strategies have been followed, among them the development of selective **COX-2** inhibitors. Our strategy to find compds. that are active on the one hand and tolerated by the GI tract on the other hand, is based on the shunt to leukotrienes. This theory is founded upon the fact that NSAIDs, while inhibiting the cyclooxygenase branch of the arachidonic acid cascade, are able to increase the 5-lipoxygenase (5-LOX) branch of arachidonic acid metab. This shunt to the 5-LOX side leads to the increase in chemotactic LTB4 and vasoconstrictive peptidoleukotrienes, the contributory effects of which to gastrointestinal disorders are widely accepted. Therefore, the design of anti-inflammatory compds. with 5-LOX inhibitory effects seems reasonable. With the compd. ML3000, this theory has gained further evidence. ML3000 is an anti-inflammatory compd. with potent activity in various animal expts. that represent models for acute and chronic

inflammation, pain, fever and **asthma**. It is a balanced inhibitor of the enzymes 5-LOX and COX-1/2 in the submicromolar range. The compd. demonstrates excellent gastrointestinal tolerance in various animal species. The preclin. profile of ML3000, which is currently in Phase III clin. development, is presented in this publication.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:554475 HCAPLUS
DOCUMENT NUMBER: 135:313019
TITLE: Current issues on the safety of non-prescription NSAIDs
AUTHOR(S): Volans, Glyn
CORPORATE SOURCE: Medical Toxicology Unit, Guy's and St. Thomas' Hospital Trust and King's College, London, SE14 5ER, UK
SOURCE: Inflammopharmacology (2001), 9(1-2), 43-49
CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with refs. There is a continuing need to monitor the safety of non-prescription (OTC) NSAIDs in order to better define known adverse drug reactions; to consider potential drug interactions and to assess the case for further OTC transfers. Recent reviews at the Medical Toxicol. Unit have therefore included: (1) the potential of NSAIDs to induce **asthma** with a view to producing guidelines for safe usage; (2) the possibility of interactions between NSAIDs and alc.; (3) the safety of **COX-2** inhibitors in overdosage.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:411272 HCAPLUS
DOCUMENT NUMBER: 136:240847
TITLE: Anti-inflammatory drugs: new multitarget compounds to face an old problem. The dual inhibition concept
AUTHOR(S): Celotti, Fabio; Laufer, Stefan
CORPORATE SOURCE: Institute of Endocrinology, University of Milano, Italy
SOURCE: Pharmacological Research (2001), 43(5), 429-436
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. In this short review we have tried to focus on some new relevant aspects of the pharmacol. control of inflammation. The clin. availability of new drugs able to produce a selective inhibition of type 2 cyclooxygenase (**COX-2**), the enzyme thought to be mainly responsible for generating arachidonic-acid-derived inflammatory mediators, has been the origin of much hope. However, expectations of having an effective and completely safe non-steroidal anti-inflammatory drug (NSAID) have been only partially fulfilled. Emerging information has challenged some aspects of the original hypothesis indicating **COX-2** as devoid of 'housekeeping' physiol. functions. Moreover, the recently available clin.

studies have indicated only a relatively small improvement in the tolerability of the newer 'selective' **COX-2** inhibitors over the classical COX-1/**COX-2** mixed type NSAIDs. The new appreciation of the role of other arachidonic acid derivs., the leukotrienes (LTS), in producing and maintaining inflammation has generated considerable interest in drugs able to block LTS receptors or to produce a selective inhibition of 5-lipoxygenase (5-LO), the initial key enzyme of the leukotriene pathway. These drugs are now included among the effective therapies of **asthma** but appear, in the few clin. studies performed, to be an insufficient single therapeutic approach in other inflammatory diseases. Drugs able to block equally well both COX and 5-LO metabolic pathways (dual inhibitors) have been developed and exptl. evaluated in the last few years, but none are available on the market yet. The pharmacol. rationale at the basis of their development is strong, and animal studies are indicative of a wide range of anti-inflammatory activity. What appears most impressive from the available studies on dual inhibitors is their almost complete lack of gastric toxicity, the most troublesome side effect of NSAIDs. The mechanism of the gastric-sparing properties of these drugs is not yet completely understood; however, it appears that leukotrienes significantly contribute to gastric epithelial injury particularly when these compds. represent the major arachidonic acid derivs. present in the gastric mucosa after inhibition of prostanoid prodn. (c) 2001 The Italian Pharmacological Society.

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:400485 HCAPLUS
DOCUMENT NUMBER: 136:160669
TITLE: Recent progress in aspirin-induced **asthma**
AUTHOR(S): Sakakibara, Hiroki
CORPORATE SOURCE: Department of Allergy and Internal Medicine, Fujita Health and Hygiene University, Japan
SOURCE: Annual Review Kokyuki (2000) 82-92
CODEN: ARKNC8
PUBLISHER: Chugai Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review. Aspirin-induced **asthma** (AIA) is a distinct clin. syndrome in which bronchoconstrictive responses to nonsteroidal anti-inflammatory drugs (NSAIDs) can be predicted on the basis of their in vitro activity as inhibitors of cyclooxygenase, i.e. AIA is assocd. with alterations in arachidonate metab. In this review, several explanations are presented including peptidoleukotrienes overprodn., overexpression of leukotriene C4 (LTC4) synthase in bronchial cells, 5-lipoxygenase and LTC4 synthase gene promoter polymorphism, PGE2 dependency, role of the mast cells, and specific **COX-2** inhibitors.

L2 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:598134 HCAPLUS
DOCUMENT NUMBER: 134:50880
TITLE: New selective **COX-2** inhibitors
AUTHOR(S): Kam, P. C. A.; Power, I.
CORPORATE SOURCE: Department of Anaesthesia and Pain Management, Royal North Shore Hospital, University of Sydney, St

Leonards, 2065, Australia
SOURCE: Pain Reviews (2000), 7(1), 3-13
CODEN: PAREFV; ISSN: 0968-1302
PUBLISHER: Arnold, Hodder Headline
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 56 refs. Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both of the cyclooxygenase (COX-1, and **COX-2**) enzymes to varying degrees; consequently, they impair prostaglandin prodn. in all tissues, causing adverse effects, esp. in the gastrointestinal tract, respiratory system (aspirin-induced **asthma**), kidney and haematol. system. Unfortunately, side-effects are common when these nonselective NSAIDs are given and many patients have contraindications to their use. The anti-inflammatory actions of the NSAIDs are mediated by **COX-2** inhibition, while the adverse effects are considered to be predominantly caused by COX-1 inhibition. Therefore, the selective inhibition of **COX-2** inhibitors offers real hope for safer NSAIDs; specific agents have now been developed to do this. Selective **COX-2** inhibitors are effective anti-inflammatory agents, but their analgesic efficacy is still unclear. While they have significantly less gastrointestinal and antiplatelet effects, the acute renal and pulmonary effects of selective **COX-2** inhibitors have not been fully clarified. Moreover, there are issues concerning their long-term safety because the inhibition of constitutive **COX-2**, which appears to have some important physiol. functions, may still cause adverse effects.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:396789 HCAPLUS
DOCUMENT NUMBER: 131:210723
TITLE: New highly selective **COX-2** inhibitors
AUTHOR(S): Ford-Hutchinson, A. W.
CORPORATE SOURCE: Merck Frosst Centre for Therapeutic Research, Kirkland, QC, H9H 3L1, Can.
SOURCE: Selective COX-2 Inhibitors: Pharmacology, Clinical Effects and Therapeutic Potential, Proceedings of a Conference, Cannes, Fr., Mar. 20-21, 1997 (1998), Meeting Date 1997, 117-125. Editor(s): Vane, John R.; Botting, Jack H. Kluwer: Dordrecht, Neth.
CODEN: 67UBAO
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review, with 55 refs. Cyclooxygenase (prostaglandin G/H-synthase, COX) exists in two isoforms which have been termed COX-1 (constitutive enzyme) and **COX-2** (an inducible enzyme). The most significant differences between **COX-2** and COX-I are in their regulation as **COX-2** can be induced transiently over a >50 fold range by a variety of inflammatory mediators as well as stimuli such as hypoxia, synaptic excitation, injury and laminar sheer stress, and simply by incubation of tissues in vitro. The mechanism of action of non-steroidal anti-inflammatory drugs involves inhibition of COX. In addn., inhibition of the prodn. of prostaglandins (PGs) explains the anti-inflammatory, analgesic and anti-pyretic activity of these compds. as well as their ability to inhibit hormone-induced uterine contractions and certain types of cancer growth. It is also abundantly clear that non-steroid anti-inflammatory drugs (NSAIDs) have mechanism-based side effects which include induction of gastrointestinal lesions, effects on renal function in compromised individuals, increases

in bleeding time, induction of NSAID-induced **asthma** and prolongation of gestation and labor. Thus, it is clear that prostanoids have both physiol. and pathol. effects. The hypothesis behind the development of selective **COX-2** inhibitors is that the therapeutic usefulness of NSAIDs will be largely due to inhibition of inducible **COX-2**, while the side effect profile will be mainly due to inhibition of COX-I. All the NSAIDs currently on the market in North America show no significant degree of selectivity for **COX-2**. Preclin. and early clin. data supports the hypothesis that selective **COX-2** inhibitors will have anti-inflammatory, analgesic and anti-pyretic activities comparable to NSAIDs with a substantial redn. in some of the side effects assocd. with this class of drugs, particularly induction of gastric lesions and effects on bleeding times. The effects of selective **COX-2** inhibitors on renal function in renally-compromised individuals remains to be detd. Mechanistic studies indicate that a high degree of in vitro biochem. selectivity for **COX-2** will be required in order to achieve effective functional selectivity in vivo.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:339261 HCAPLUS
DOCUMENT NUMBER: 131:138793
TITLE: CI-1004 Parke-Davis & Co
AUTHOR(S): Marchini, Francesco
CORPORATE SOURCE: Zambon Group Spa, Milan, Italy
SOURCE: Current Opinion in Anti-Inflammatory and Immunomodulatory Investigational Drugs (1999), 1(1), 64-68
CODEN: COAIFF; ISSN: 1464-8474
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with many refs. CI-1004 (PD-136095) is a dual inhibitor of lipoxygenase and cyclooxygenase 2 (**COX-2**) that is under development by Parke-Davis as a potential treatment for inflammatory diseases such as **asthma**. Phase II trials have been initiated; phase III trials for osteo- and rheumatoid arthritis were scheduled to commence by the end of 1998, but by Mar. 1999 initiation of the trials had not been announced. In Feb. 1999 Morgan Stanley Dean Witter predicted sales of $50 million in 2002 rising to $325 million in 2005.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:666433 HCAPLUS
DOCUMENT NUMBER: 130:64841
TITLE: The COX-1/**COX-2** balance in **asthma**
AUTHOR(S): Pang, L.; Pitt, A.; Petkova, D.; Knox, A. J.
CORPORATE SOURCE: Respiratory Medicine Unit, City Hospital, Nottingham, UK
SOURCE: Clinical and Experimental Allergy (1998), 28(9), 1050-1058
CODEN: CLEAEN; ISSN: 0954-7894
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English
AB A review, with 75 refs. The role of cyclo-oxygenase products in regulating airway function and the COX balance in **asthma** is reviewed.
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1998:300340 HCAPLUS
DOCUMENT NUMBER: 129:107217
TITLE: Cyclooxygenase-2 expression in airway cells
AUTHOR(S): Barnes, Peter J.; Belvisi, Maria G.; Newton, Robert; Mitchell, Jane A.
CORPORATE SOURCE: Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK
SOURCE: Lung Biology in Health and Disease (1998), 114(Eicosanoids, Aspirin, and Asthma), 111-127
CODEN: LBHDD7; ISSN: 0362-3181
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 82 refs., on prostanoids in airways; induction of cyclooxygenase (**COX-2**) in airway cells; regulation of **COX-2**; and relevance in **asthma**.
REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1997:49357 HCAPLUS
DOCUMENT NUMBER: 126:102650
TITLE: Biochemical makers of inflammatory cell activation in bronchoalveolar lavage
AUTHOR(S): Triggiani, M.; Oriente, A.; De Marino, V.; Sofia, M.; Carratu, L.; Marone, G.
CORPORATE SOURCE: Cattedra Immunologia Clinica Allergologia, Univ. Federico II, Naples, Italy
SOURCE: Immunologia '95, Atti del Congresso Nazionale della Societa Italiana di Immunologia e Immunopatologia, 14th, Bari, Italy, Oct. 1-4, 1995 (1995), 65-69. Editor(s): Dammacco, Franco. Monduzzi Editore: Bologna, Italy.
CODEN: 63WGAL
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: Italian
AB A review with 24 refs. Topics discussed include: selective biochem. function of arachidonic acid metabolites. in cellular inflammation and secretion of enzymes implicated in the metab. of lipid mediators involved in cellular inflammation (PLA2, COX-1, **COX-2**).

L2 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1996:686881 HCAPLUS
DOCUMENT NUMBER: 126:102578
TITLE: Airway epithelium in allergic inflammation
AUTHOR(S): Takizawa, Hajime

CORPORATE SOURCE: Fac. Med., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Igaku no Ayumi (1996), 179(3), 173-176
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review, with 16 refs., on the enhancement of inflammation by cytokines secreted from airway epithelial cells and suppression of the cytokine prodn. by therapeutic drugs, enhancement of the expression of cyclooxygenase-2 (**COX-2**) by cytokines and suppression by steroids, suppression of endothelin-1 prodn. in airway epithelial cells by steroids and erythromycin, and suppression of inducible NO synthetase by glucocorticoid. Cytokines enhance migration, activation and elongation of life of neutrophils, and neutrophil adhesion. Tumor growth factor β (TGFβ) is an important factor in mucus healing reaction and remodeling in **asthma**. The expression of human lymphocytic antigen (HLA) class II in the epithelial cells and the presence of Langerhans' cells play some roles in airway immune reaction in **asthma**.

L2 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1996:159889 HCAPLUS
DOCUMENT NUMBER: 124:277463
TITLE: Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs
AUTHOR(S): Senna, Gian E.; Passalacqua, Giovanni; Andri, Giovanni; Dama, Anna R.; Albano, Monica; Fregonese, Laura; Andri, Luigi
CORPORATE SOURCE: Allergy Unit, Verona General Hospital, Verona, Italy
SOURCE: Drug Safety (1996), 14(2), 94-103
CODEN: DRSAEA; ISSN: 0114-5916
PUBLISHER: Adis
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 73 refs. Aspirin (acetylsalicylic acid) and other NSAIDs are responsible for many adverse effects. Among them, pseudo-allergic reactions (urticaria/angioedema, **asthma**, anaphylaxis) affect up to 9% of the population and up to 30% of **asthmatic** patients. The mechanisms provoking these reactions have not been fully elucidated, but it appears that inhibition of cyclo-oxygenase (COX) plays a central role. The anti-inflammatory action of nimesulide differs from that of other NSAIDs, possibly because of its chem. structure. In particular, nimesulide is selective for **COX-2** and displays addnl. properties in terms of its effects on inflammatory mediator synthesis and release. For these reasons, nimesulide is generally well tolerated by NSAID-intolerant patients and patients with NSAID-induced **asthma**. The good tolerability of nimesulide as an alternative drug for use in patients with NSAID intolerance has been demonstrated in a large no. of clin. studies.

=>

ACCESSION NUMBER: 2001:411272 HCAPLUS
DOCUMENT NUMBER: 136:240847
TITLE: Anti-inflammatory drugs: new multitarget compounds to face an old problem. The dual inhibition concept
AUTHOR(S): Celotti, Fabio; Laufer, Stefan
CORPORATE SOURCE: Institute of Endocrinology, University of Milano, Italy
SOURCE: Pharmacological Research (2001), 43(5), 429-436
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. In this short review we have tried to focus on some new relevant aspects of the pharmacol. control of inflammation. The clin. availability of new drugs able to produce a selective inhibition of type 2 cyclooxygenase (**COX-2**), the enzyme thought to be mainly responsible for generating arachidonic-acid-derived inflammatory mediators, has been the origin of much hope. However, expectations of having an effective and completely safe non-steroidal anti-inflammatory drug (NSAID) have been only partially fulfilled. Emerging information has challenged some aspects of the original hypothesis indicating **COX-2** as devoid of 'housekeeping' physiol. functions. Moreover, the recently available clin. studies have indicated only a relatively small improvement in the tolerability of the newer 'selective' **COX-2** inhibitors over the classical COX-1/**COX-2** mixed type NSAIDs. The new appreciation of the role of other arachidonic acid derivs., the leukotrienes (LTS), in producing and maintaining inflammation has generated considerable interest in drugs able to block LTS receptors or to produce a selective inhibition of 5-lipoxygenase (5-LO), the initial key enzyme of the leukotriene pathway. These drugs are now included among the effective therapies of **asthma** but appear, in the few clin. studies performed, to be an insufficient single therapeutic approach in other inflammatory diseases. Drugs able to block equally well both COX and 5-LO metabolic pathways (dual inhibitors) have been developed and exptl. evaluated in the last few years, but none are available on the market yet. The pharmacol. rationale at the basis of their development is strong, and animal studies are indicative of a wide range of anti-inflammatory activity. What appears most impressive from the available studies on dual inhibitors is their almost complete lack of gastric toxicity, the most troublesome side effect of NSAIDs. The mechanism of the gastric-sparing properties of these drugs is not yet completely understood; however, it appears that leukotrienes significantly contribute to gastric epithelial injury particularly when these compds. represent the major arachidonic acid derivs. present in the gastric mucosa after inhibition of prostanoid prodn. (c) 2001 The Italian Pharmacological Society.
REFERENCE COUNT: 101

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L21 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:857962 HCAPLUS
DOCUMENT NUMBER: 138:135283
TITLE: The role of cyclooxygenases and prostaglandins in the pathogenesis of rheumatoid arthritis
AUTHOR(S): Stanczyk, Joanna; Kowalski, Marek Leszek
CORPORATE SOURCE: Katedra Immunol. i Zakl. Immunol. Klin., Akad. Med., Lodz, 92-213, Pol.
SOURCE: Polski Merkuriusz Lekarski (2001), 11(65), 438-443
CODEN: PMLOB9; ISSN: 1426-9686
PUBLISHER: Medpress
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Polish

AB A review. Rheumatoid arthritis (RA) is a systemic inflammatory disease with polyarticularsynovitis leading to formation of rheumatoid pannus and subsequent erosion of articular cartilage and bone. Prostaglandins (PGs) - a group of arachidonic acid metabolites found at elevated levels in synovial fluid and synovial membrane are considered to play a pivotal role in development of vasodilatation, fluid extravasation and pain in synovial tissues. Moreover, there is increasing evidence that PGs (esp. prostaglandin E2) are mediators involved in complex interactions leading to development of erosions of articular cartilage and juxta-articular bone. Cyclooxygenase is an enzyme playing crucial role in PG prodn. It is known that two forms of cyclooxygenase exist: cyclooxygenase-1 (COX-1) playing house-keeping functions and cyclooxygenase-2 (COX-2) involved in inflammatory responses. Synovial tissues from patients with RA are shown to contain COX-2 and to a less extent COX-1. COX-2 expression in rheumatoid synovium is induced by proinflammatory cytokines, mainly IL-1, while corticosteroids are capable of inhibiting COX-2 expression. The understanding of crucial role of COX-2 in synovial inflammation led to development of new group of anti-inflammatory agents - selective **COX-2 inhibitors**, that inhibit specifically COX-2, providing effective anti-inflammatory action without the side effects assocd. with inhibition of COX-1. In the context of widespread use of selective **COX-2 inhibitors** hypothetical role of COX-1 in RA pathol. should be elucidated.

L21 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:292839 HCAPLUS
DOCUMENT NUMBER: 129:80257
TITLE: Expression and regulation of COX-2 in synovial tissues of arthritic patients
AUTHOR(S): Crofford, L. J.
CORPORATE SOURCE: Department of Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Improved Non-Steroid Anti-Inflammatory Drugs: COX-2 Enzyme Inhibitors, Proceedings of a Conference, London, Oct. 10-11, 1995 (1996), Meeting Date 1995, 133-143. Editor(s): Vane, John R.; Botting, Jack H.; Botting, Regina M. Kluwer: Dordrecht, Neth.
CODEN: 65ZRAF
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review, with 44 refs. Available data regarding expression and

regulation of cyclooxygenase (COX)-2 in synovial tissue is summarized. The pot. importance of a highly regulated enzyme in the prostaglandin synthetic pathway for rapid and highly localized prodn. of prostaglandins is discussed. Finally, the author speculates on the role of COX-2 in the pathogenesis of inflammatory **synovitis** and the pot. for specific **COX-2 inhibitors** as treatments for chronic inflammatory arthritis.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1997:645437 HCAPLUS
DOCUMENT NUMBER: 127:305964
TITLE: Expression and regulation of cyclooxygenase-2 in synovial tissues of arthritic patients
AUTHOR(S): Crofford, L. J.
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor, MI, 48109-0531, USA
SOURCE: New Targets in Inflammation: Inhibitors of COX-2 or Adhesion Molecules, Proceedings of a Conference, New Orleans, Apr. 15-16, 1996 (1996), 83-91. Editor(s): Bazan, Nicolas G.; Botting, Jack H.; Vane, John R. Kluwer: Dordrecht, Neth.
CODEN: 65DFA5
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review, with 30 refs. The available data regarding expression and regulation of COX-2 in synovial tissues are summarized. The role of COX-2 in the pathogenesis of the inflammatory **synovitis** of rheumatoid arthritis and the potential for **COX-2 inhibitors** in the treatment of chronic inflammatory arthritis are discussed.

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14021 COX
(COX OR COXES)
8089424 2
6712 COX-2
(COX(W)2)
884500 INHIBITOR?
L1 2462 COX-2 (W) INHIBITOR?

=> s l1 and fever
24465 FEVER
600 FEVERS
24635 FEVER
(FEVER OR FEVERS)
L2 86 L1 AND FEVER

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1741568 REVIEW/DT
L3 18 L2 AND REVIEW/DT

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L3 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:897168 HCAPLUS
DOCUMENT NUMBER: 139:357613
TITLE: Clinical application of **COX-2 inhibitors**
AUTHOR(S): Kawai, Shinichi
CORPORATE SOURCE: Incurable Dis. Res. Cent., St. Marianna Univ. Sch. Med., Japan
SOURCE: Ensho to Men'eki (2003), 11(6), 709-716
CODEN: ENMEFA; ISSN: 0918-8371
PUBLISHER: Sentan Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review on (1) physiol. functions and expression of cyclooxygenase-1 (COX-1) and COX-2, (2) COX inhibition and other actions of NSAIDs, (3) classification of NSAIDs based on COX-2 selectivity, (4) clin. application of **COX-2 inhibitors** (celecoxib, rofecoxib, etc.) in the treatment of rheumatoid arthritis, pain, **fever**, patent ductus arteriosus, tumors, and other diseases, and (5) adverse effects of selective **COX-2 inhibitors** (gastrointestinal toxicity, nephrotoxicity, etc.).

L3 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:845170 HCAPLUS
DOCUMENT NUMBER: 140:331487
TITLE: Non steroidal anti-inflammatory drugs and **COX-2 inhibitors** as anti-cancer therapeutics: hypes, hopes and reality

AUTHOR(S): Rueegg, Curzio; Zaric, Jelena; Stupp, Roger
CORPORATE SOURCE: Centre Pluridisplinaire d'Oncologie, University of Lausanne Medical School, Lausanne, CH-1066, Switz.
SOURCE: Annals of Medicine (Basingstoke, United Kingdom) (2003), 35(7), 476-487
CODEN: ANMDEU; ISSN: 0785-3890
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Non-steroidal anti-inflammatory drugs (NSAIDs) and specific inhibitors of cyclooxygenase (COX)-2, are therapeutic groups widely used for the treatment of pain, inflammation and **fever**. There is growing exptl. and clin. evidence indicating NSAIDs and **COX-2 inhibitors** also have anti-cancer activity. Epidemiol. studies have shown that regular use of Aspirin and other NSAIDs reduces the risk of developing cancer, in particular of the colon. Mol. pathol. studies have revealed that COX-2 is expressed by cancer cells and cells of the tumor stroma during tumor progression and in response to chemotherapy or radiotherapy. Exptl. studies have demonstrated that COX-2 over expression promotes tumorigenesis, and that NSAIDs and **COX-2 inhibitors** suppress tumorigenesis and tumor progression. Clin. trials have shown that NSAIDs and **COX-2 inhibitors** suppress colon polyp formation and malignant progression in patients with familial adenomatous polyposis (FAP) syndrome. Recent advances in the understanding of the cellular and mol. mechanisms of the anti-cancer effects of NSAIDs and **COX-2 inhibitors** have demonstrated that these drugs target both tumor cells and the tumor vasculature. The therapeutic benefits of **COX-2 inhibitors** in the treatment of human cancer in combination with chemotherapy or radiotherapy are currently being tested in clin. trials. In this article we will review recent advances in the understanding of the anti-tumor mechanisms of these drugs and discuss their potential application in clin. oncol.

REFERENCE COUNT: 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:749505 HCAPLUS
DOCUMENT NUMBER: 140:138457
TITLE: Cyclooxygenase-2 biology
AUTHOR(S): Claria, Joan
CORPORATE SOURCE: DNA Unit, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Universitat de Barcelona, Barcelona, 08036, Spain
SOURCE: Current Pharmaceutical Design (2003), 9(27), 2177-2190
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. In mammalian cells, eicosanoid biosynthesis is usually initiated by the activation of phospholipase A2 and the release of arachidonic acid from membrane phospholipids in response to the interaction of a stimulus with a receptor on the cell surface. Arachidonic acid is subsequently transformed by the enzyme cyclooxygenase (COX) to prostaglandins (PGs) and thromboxane (TX). The COX pathway is of particular clin. relevance because it is the major target for non-steroidal anti-inflammatory drugs, which are commonly used for relieving inflammation, pain and **fever**. In 1991, it was disclosed that COX exists in two distinct isoenzymes (COX-1 and COX-2), one of which,

COX-2, is primarily responsible for inflammation but apparently not for gastrointestinal integrity or platelet aggregation. For this reason, in recent years, novel compds. that are selective for this isoenzyme, the so-called selective **COX-2 inhibitors** or COXIBs, which retain anti-inflammatory activity but minimize the risk of gastrointestinal toxicity and bleeding, have been developed. This review article provides an overview and an update on the progress achieved in the area of COX-2 and PG biosynthesis and describes the role of COX-2 in health and disease. It also discusses some unresolved issues related to the use of selective **COX-2 inhibitors** as a safe and promising therapeutic option not only for the treatment of inflammatory states but also for cancer.

REFERENCE COUNT: 159 THERE ARE 159 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:710340 HCAPLUS
DOCUMENT NUMBER: 140:2168
TITLE: The structure of mammalian cyclooxygenases
AUTHOR(S): Garavito, R. Michael; Mulichak, Anne M.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI, 48824-1319, USA
SOURCE: Annual Review of Biophysics and Biomolecular Structure (2003), 32, 183-206
CODEN: ABBSE4; ISSN: 1056-8700
PUBLISHER: Annual Reviews Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Cyclooxygenases-1 and -2 (COX-1 and COX-2, also known as prostaglandin H2 synthases-1 and -2, resp.) catalyze the committed step in prostaglandin synthesis. COX-1 and -2 are of particular interest because they are the major targets of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen, and the new COX-2-selective inhibitors. Inhibition of the COXs with NSAIDs acutely reduces inflammation, pain, and **fever**, and long-term use of these drugs reduces the incidence of fatal thrombotic events, as well as the development of colon cancer and Alzheimer's disease. Here, the authors examine how the structures of COXs relate mechanistically to cyclooxygenase and peroxidase catalysis and how alternative fatty acid substrates bind within the COX active site. The authors further examine how NSAIDs interact with COXs and how differences in the structure of COX-2 result in enhanced selectivity toward **COX-2 inhibitors**.

REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:515293 HCAPLUS
DOCUMENT NUMBER: 139:390478
TITLE: Cyclooxygenase-2 inhibitors
AUTHOR(S): Gajraj, Noor M.
CORPORATE SOURCE: Eugene McDermott Center for Pain Management, Department of Anesthesiology and Pain Management, U.T. Southwestern Medical Center, Dallas, TX, USA
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (2003), 96(6), 1720-1738

CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Cyclooxygenase-2 is thought to be involved in pathophysiol. processes such as inflammation, pain, and **fever**. This led to the development of currently available selective **COX-2 inhibitors** celecoxib, rofecoxib, and valdecoxib. These drugs have analgesic efficacy comparable with that of conventional nonsteroidal antiinflammatory drugs (NSAIDs). In addn., they have no antiplatelet activity at therapeutic dosages and may be assocd. with reduced gastrointestinal (GI) side effects compared with conventional NSAIDs such as ibuprofen.
REFERENCE COUNT: 230 THERE ARE 230 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2003:331332 HCAPLUS
DOCUMENT NUMBER: 139:270087
TITLE: Cyclooxygenases. II. Nonsteroidal anti-inflammatory drugs as their inhibitors
AUTHOR(S): Kolaczkowska, Elzbieta
CORPORATE SOURCE: Zakl. Immunol. Ewolucyjnej, Inst. Zool., Uniw. Jagiellonski, Krakow, 30-060, Pol.
SOURCE: Postepy Biologii Komorki (2002), 29(4), 555-578
CODEN: PBKODV; ISSN: 0324-833X
PUBLISHER: Fundacja Biologii Komorki i Biologii Molekularnej
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Polish
AB A review. Since its discovery in 1897, aspirin (acetylsalicylic acid) was the most important and common anti-inflammatory, analgesic and anti-pyretic drug throughout the 20th century. Aspirin and aspirin-like drugs, commonly named nonsteroidal anti-inflammatory drugs (NSAID), exert their action through inhibition of cyclooxygenase enzymes. Cyclooxygenase exists in at least 2 isoforms, the constitutive COX-1 and inducible COX-2. Aspirin and other classical NSAID drugs inhibit both isoforms. Prostaglandins produced by the COX-1 activity protect gastrointestinal mucosa and inhibition of this enzyme isoform leads to stomach and duodenum ulceration. To prevent ulcer development, mucosal coating drugs can be co-administered, or classical NSAID drugs may be substituted by NSAID agents releasing nitric oxide or assocd. with zwitterionic phospholipids. Recent studies led to development of selective **COX-2 inhibitors** acting only on COX-2 that is involved in inflammation and pain. New generation of NSAID drugs is safer but not free of side-effects that are due to constitutive expression of COX-2 in the kidneys, healing ulcers, and reproductive tract. Some studies, including those on paracetamol, imply the existence of the third COX isoform (COX-3). The mechanism of paracetamol action remains unknown. Paracetamol decreases pain and **fever**, but not inflammation, and has low selectivity for COX-1 and COX-2; this seems to confirm the COX-3 hypothesis. These discoveries changed the pharmacol. position of aspirin. Low-dose aspirin is currently recommended as an anti-thrombotic drug since blood platelets contain exclusively COX-1.

L3 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2001:907086 HCAPLUS

DOCUMENT NUMBER: 136:177365
TITLE: **COX-2 inhibitors** compared and contrasted
AUTHOR(S): Bennett, Alan; Tavares, Ignatius A.
CORPORATE SOURCE: Academic Department of Surgery, The Rayne Institute, Guy's, King's and St Thomas' School of Medicine, King's College, London, UK
SOURCE: Expert Opinion on Pharmacotherapy (2001), 2(11), 1859-1876
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Non-steroidal anti-inflammatory drugs (NSAIDs) are the principal drug treatments for inflammation, pain and **fever**. They act primarily by inhibiting prostaglandin (PG) synthesis but this can cause adverse events (AEs). Since the discovery of two PG synthesizing enzymes, COX-1 and COX-2, and the substantial evidence that sparing COX-1 is advantageous for gastric safety, great interest has focused on selective **COX-2 inhibitors**. Much of the impetus has come from the most recently developed compds. celecoxib and rofecoxib, which have shown spectacular sales growth. However, the older drugs etodolac, nimesulide and meloxicam, made before COX-2 was discovered, are also COX-1-sparing and have good GI safety and therapeutic activities. These five compds. show similarities and differences that are discussed in relation to aspects that include their uses, efficacy, actions and safety.

REFERENCE COUNT: 158 THERE ARE 158 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:263605 HCAPLUS
DOCUMENT NUMBER: 135:70473
TITLE: Novel serotonergic and non-serotonergic migraine **headache** therapies
AUTHOR(S): Slassi, Abdelmalik; Isaac, Methvin; Arora, Jalaj
CORPORATE SOURCE: Discovery Chemistry Department, NPS Allelix Corp., Mississauga, ON, L4V 1V7, Can.
SOURCE: Expert Opinion on Therapeutic Patents (2001), 11(4), 625-649
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 196 refs. In the last four years discovery of pharmacotherapeutic treatments for migraine **headaches** has received much attention. Since the patent literature was last reviewed in 1997 [1], advances have been made in the understanding of mechanism and pathophysiol. of migraine. Introduction of sumatriptan to the market has led to acceleration in research efforts towards finding safe and effective treatments for migraine. The importance of this field is evidenced by the no. of compds. in clin. trials and by the no. of patents filed in recent years. For example, besides sumatriptan, a second generation of three new drugs (naratriptan [2], zolmitriptan [3] and rizatriptan [4]) has entered the marketplace and few others are presently in clin. evaluation. In addn., classical drug design has yielded highly potent and selective ligands to target relevant receptor subtypes in migraine treatment. This article highlights and reviews the research advances published in patent literature between Jan. 1997 through Nov. 2000. The article is supplemented with selected refs. on design and development of novel agents with which to treat migraine and to study its mechanism and pathophysiol. Emphasis is made on serotonergic agents, namely serotonin (5-hydroxytryptamine, 5-HT) receptor subtype (5-HT1D, 5-HT1F and 5-HT5) agonists, drug combinations (e.g., 5-HT1D agonists with **COX-2 inhibitors** or NSAIDs), tachykinin receptor (NK1) antagonists and GABAergic agents. Also included are patents describing chem. entities that may be effective in migraine therapy based on their pharmacol. actions as anticonvulsants, LTD4 receptor blocker agents and thromboxane inhibitors. By no means has any attempt been made to exhaustively review the literature; but rather, primary refs. along with citations to latest literature reviews have been included in each section.

L10 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:554480 HCAPLUS
DOCUMENT NUMBER: 135:326832
TITLE: The clinical developments and future of the **COX-2 inhibitor** drugs
AUTHOR(S): Goldstein, Jerome
CORPORATE SOURCE: San Francisco Clinical Research Center, San Francisco, CA, 94109, USA
SOURCE: Inflammopharmacology (2001), 9(1-2), 91-99
CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with refs. A new era of analgesia began with the discovery of aspirin in 1899. Since that time, many newer NSAIDs (non-steroid anti-inflammatory drugs) have been discovered and utilized in clin. practice. The mechanism of anti-inflammatory action of NSAIDs is believed to result from inhibition of the enzyme cyclooxygenase (COX), discovered in the 1970s. This enzyme represents the key rate-limiting step in the prodn. of prostaglandins (PGs) from arachidonic acid. Since PGs are essential for normal gastrointestinal, renal, and platelet function, as well as mediating the inflammatory process, inhibition of cyclooxygenase has both beneficial and deleterious effects. The beneficial effect, obviously, is inhibition of the inflammatory process, while the harmful effects comprise an increased incidence of upper gastrointestinal toxicity (ulceration, perforation, and bleeding) as well as possible renal and platelet dysfunction. In the late 1980s, it was discovered that two isoforms of cyclooxygenase existed (COX-1 and COX-2). COX-1 represents a constitutive form that is expressed in most tissues. In contrast, COX-2 is induced at sites of inflammation and also occurs under normal circumstances in the brain and renal tissues. Since COX-2 levels increase dramatically during acute and chronic inflammation, it was hypothesized that the **COX-2 inhibitors** might offer significant anti-inflammatory qualities with reduced toxicity and may have utility in central nervous system mediated conditions other than peripheral pain, including dementias such as Alzheimer's disease and **headache**, specifically, migraine **headache**.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:649617 HCAPLUS
DOCUMENT NUMBER: 136:79074
TITLE: The coxibs, selective inhibitors of cyclooxygenase-2
AUTHOR(S): Wood, Alastair J. J.; FitzGerald, Garret A.; Patrono, Carlo
CORPORATE SOURCE: Center for Experimental Therapeutics, University of Pennsylvania, Philadelphia, PA, 19104-6084, USA
SOURCE: New England Journal of Medicine (2001), 345(6), 433-442
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review on the development of coxibs as an alternative to nonsteroidal antiinflammatory drugs (NSAID) for treating arthritis, menstrual pain, and **headache**. Both groups of drugs inhibit prostaglandin G/H synthase, the enzyme that catalyzes the transformation of arachidonic acid to a range of lipid mediators, termed prostaglandins and thromboxanes. However, whereas NSAIDs inhibit the two recognized forms of the enzyme, referred to as cyclooxygenase-1 and cyclooxygenase-2, the coxibs are selective inhibitors of cyclooxygenase-2. Since the inhibition of cyclooxygenase-2 has been more directly implicated in ameliorating inflammation, it was hoped that coxibs would be better tolerated than nonselective NSAIDs but equally efficacious.

L21 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:266015 HCAPLUS
DOCUMENT NUMBER: 135:40287
TITLE: The status of ongoing trials for **mild cognitive impairment**
AUTHOR(S): Sramek, John J.; Veroff, Amy E.; Cutler, Neal R.
CORPORATE SOURCE: California Clinical Trials, Beverly Hills, CA, USA
SOURCE: Expert Opinion on Investigational Drugs (2001), 10(4), 741-752
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 82 refs. **Mild cognitive impairment** (MCI) is a term used to describe memory decline or other specific cognitive impairment in individuals who do not have dementia or significant impairment of other cognitive functions beyond that expected for their age or education. It has been suggested that as much as 38% of the elderly population would meet criteria for MCI and although the assocd. memory deficits are mild, the fact that up to 15% of MCI patients, particularly those with a particular type of memory impairment, convert to Alzheimer's disease (AD) annually has prompted serious attention. Despite the high conversion rate, MCI cannot be used synonymously with early or mild AD, as patients with AD are impaired not only in memory performance but in other cognitive domains as well; they meet diagnostic criteria for dementia. However, since there is a high conversion rate from MCI to AD, it is likely many with MCI have the underlying neuropathol. of AD, though they do not yet meet clin. diagnostic criteria. Therefore, treatment strategies developed for AD, specifically acetylcholinesterase inhibitors and **Cox-2 inhibitors**, have been among the first employed to treat MCI. It is hoped that by impeding the progression of MCI in this manner, fewer patients will convert to AD. This article will give a brief overview of the condition of **mild cognitive impairment** and an account of trial methodol. and current treatment strategies being employed for MCI.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT